ehp ENVIRONMENTAL HEALTH PERSPECTIVES
http://www.ehponline.org

Airborne Fine Particles and Risk of Hospital Admissions for Understudied Populations: Effects by Urbanicity and Short-Term Cumulative Exposures in 708 U.S. Counties

Mercedes A. Bravo, Keita Ebisu, Francesca Dominici, Yun Wang, Roger D. Peng, and Michelle L. Bell

http://dx.doi.org/10.1289/EHP257

Received: 14 December 2015
Revised: 12 May 2016
Accepted: 8 June 2016
Published: 20 September 2016

Environ Health Perspect DOI: 10.1289/EHP257
Advance Publication: Not Copyedited

Airborne Fine Particles and Risk of Hospital Admissions for Understudied Populations: Effects by Urbanicity and Short-Term Cumulative Exposures in 708 U.S. Counties

Mercedes A. Bravo,[1*] Keita Ebisu,[2] Francesca Dominici,[3] Yun Wang,[4] Roger D. Peng,[5] and Michelle L. Bell[6]

[1] Yale University, School of Forestry and Environmental Studies. mbravo@med.umich.edu.

[2] Yale University, School of Forestry and Environmental Studies. keita.ebisu@yale.edu.

[3] Harvard University, Biostatistics Department. fdominic@hsph.harvard.edu.

[4] Harvard University, Biostatistics Department. yunwang@hsph.harvard.edu.

[5] Johns Hopkins University, Bloomberg School of Public Health. rpeng@jhsph.edu.

[6] Michelle L. Bell, Yale University, School of Forestry and Environmental Studies. michelle.bell@yale.edu.

* Corresponding author. Current affiliation: University of Michigan, School of Natural Resources and Environment, 440 Church St., Ann Arbor, MI, 48103, USA. (734) 764-4584.

Running head: Fine particles and health in understudied US populations

Competing Financial Interests: The authors declare they have no actual or potential competing financial interests.

Financial support: The research reported in this publication was supported by the National Institutes of Health under award numbers R01ES019560 (R. Peng, M. Bell), R01ES026217, R01ES024332, R21ES024012, and P50MD010428, and with support from the Health Effects Institute (F. Dominici, Y. Wang). It was also developed under the US Environmental Protection Agency grants 83479801 (M. Bell, K. Ebisu, F. Dominici), R833863 (M. Bell, K. Ebisu, M. Bravo) and Assistance Agreement No. 83587101, awarded by the US EPA to Yale University (M. Bell, R. Peng). It has not been formally reviewed by the EPA. The views expressed in this document are solely those of its authors and do not necessarily reflect those of the Agency. EPA does not endorse any products or commercial services mentioned in this publication. The authors declare they have no actual or potential competing financial interests.

ABSTRACT

Background: Evidence of health risks associated with ambient airborne fine particles in nonurban populations is extremely limited.

Objective: We estimate risk of hospitalization associated with short-term exposures to particulate matter with an aerodynamic diameter <2.5μ ($PM_{2.5}$) in urban and nonurban counties with population ≥50,000.

Methods: We utilize a database of daily cardiovascular- and respiratory-related hospitalization rates constructed from Medicare National Claims History files (2002-2006), including 28 million Medicare beneficiaries in 708 counties. Daily $PM_{2.5}$ exposures were estimated using the Community Multiscale Air Quality (CMAQ) downscaler. We use time-series analysis of hospitalization rates and $PM_{2.5}$ to evaluate associations between $PM_{2.5}$ levels and hospitalization risk in single pollutant models.

Results: We observed an association between cardiovascular hospitalizations and same-day $PM_{2.5}$, with higher risk in urban counties: a 0.35% (95% posterior interval: -0.71%-1.41%) and 0.98% (0.73%-1.23%) increase in hospitalization risk per 10μg/m^3 increment in $PM_{2.5}$ was observed in the least urban and most urban counties, respectively. The largest association for respiratory hospitalizations, a 2.57% (0.87%-4.30%) increase per 10μg/m^3 increase in $PM_{2.5}$, was observed in the least urban counties; in the most urban counties, a 1.13% (0.73%-1.54%) increase was observed. Effect estimates for cardiovascular hospitalizations were highest for smaller lag times, while effect estimates for respiratory hospitalizations increased as more days of exposure were included.

Conclusion: In nonurban counties with population ≥50,000, exposure to $PM_{2.5}$ is associated with increased risk for respiratory hospitalizations; in urban counties, exposure is associated with

increased risk of cardiovascular hospitalizations. Effect estimates based on a single day of exposure may underestimate true effects for respiratory hospitalizations.

INTRODUCTION

Epidemiological studies have shown associations between fine particles ($PM_{2.5}$) and health outcomes such as hospital admissions and mortality (Dominici et al. 2003; Dominici et al. 2006; Kloog et al. 2014; Peng et al. 2005), but are primarily based in urban areas due to the placement of ambient monitors that provide the necessary exposure data. Consequently, the majority of $PM_{2.5}$ health effects estimates are derived from urban populations. Although toxicological, individual-, and population-level studies provide strong evidence that $PM_{2.5}$ adversely affects health, key questions remain.

Current evidence on short-term $PM_{2.5}$ exposure and health has critical limitations. First, estimates from many multi-city studies are obtained by pooling estimates from counties with monitoring data, thereby completely disregarding health effects in communities without monitoring data, which tend to be more rural (Bravo et al. 2012). Lack of monitoring data outside of urban areas precludes estimation of exposure and health effects in such locations, and as a result, it is unknown whether and to what extent health effects in monitored vs. unmonitored, or urban vs. rural, communities differ. Recently, researchers have used satellite data to estimate $PM_{2.5}$ exposures (Kloog et al. 2011; Lee et al. 2015) and health outcomes in areas without monitoring data (Hyder et al. 2014; Kloog et al. 2014).

A second limitation is that, by relying exclusively on monitoring data primarily from urban counties, studies cannot fully investigate susceptibility. Populations in urban counties differ demographically from those in nonurban (more rural) counties (Miranda et al. 2011), and may have dissimilar exposure levels or health responses to exposure. Regional and temporal differences have been observed in $PM_{2.5}$ composition and health effect estimates (Bell et al. 2007); $PM_{2.5}$ composition and time trends likely differ by urbanicity. Populations' baseline health

status and comorbidities (e.g., obesity), demographic and behavioral risk factors (e.g., tobacco use), and other factors differ between urban and nonurban communities. For example, rural communities have greater barriers to health care access (Vanasse et al. 2010), higher rates of many chronic diseases (Eberhardt and Pamuk 2004; Hartley 2004), and different activity patterns (Matz et al. 2015). Thus, $PM_{2.5}$ exposures and susceptibility may differ between urban and nonurban populations, but such differences are not captured in currently available health effect estimates.

Third, most $PM_{2.5}$ monitors sample every three days, prohibiting study of short-term cumulative exposures. Health effects of $PM_{2.5}$ may depend on both concentration and duration of exposure. Same- or single-day lags of $PM_{2.5}$ exposure may not fully capture health risk, if risk is affected by exposure experienced over multiple days, as some studies suggest (Zanobetti et al. 2003).

Previous time-series $PM_{2.5}$ studies, which are subject to the above limitations, studied up to 204 urban US counties (Bell et al. 2008; Dominici et al. 2006). We utilize output from the Community Multi-scale Air Quality (CMAQ) model downscaler to estimate daily $PM_{2.5}$ levels in monitored and non-monitored areas, for over 700 US counties for 2002-2006. With daily, downscaler-derived estimates of $PM_{2.5}$, we estimate county-specific and overall health effects associated with short-term exposure to $PM_{2.5}$ in populations excluded from previous studies. We also examine health impacts of short-term cumulative exposures, which is only possible with daily $PM_{2.5}$ estimates.

METHODS

Health data

We used files from the Centers for Medicare and Medicaid Services (CMS) to identify beneficiaries ≥65 years (y) enrolled in the Fee-for-Service plan for at least one month from January 1, 2002 to December 31, 2006. Using beneficiaries' residential ZIP code, we identified those who resided in one of study area's 795 US counties with a population ≥50,000 in the 2000 Census (U.S. Census Bureau 2000a).

We linked this dataset with CMS inpatient data to identify beneficiaries hospitalized with a principal discharge diagnosis of cardiovascular (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 390 to 459) or respiratory conditions (chronic obstructive pulmonary disease (ICD-9-CM, 490 -492) or respiratory tract infections (ICD-9 464 -466, 480 -487), from January 1, 2002 through December 31, 2006. Using dates of admission, we constructed our final sample of daily cardiovascular or respiratory hospital admission rates, aggregated at the county level (the dataset identifying beneficiaries ≥65y by county was used as the denominator in county-specific rate calculations). Of the 28,019,815 unique beneficiaries, 4,860,662 (17.3%) and 1,855,699 (6.62%) had at least one cardiovascular- or respiratory-related hospital admission, respectively, during the study period.

Exposure data

Daily (24 hour [h]) averages of $PM_{2.5}$ monitoring data (2002-2006) were obtained from the US Environmental Protection Agency (EPA) National Air Monitor Stations or State and Local Air Monitoring Stations (NAMS/SLAMS) network. Downscaler output was obtained for 2002-2006 (http://www.epa.gov/air-research/fused-air-quality-surfaces-using-downscaling-tool-predicting-daily-air-pollution). Inputs to the downscaler include monitoring data from the NAMS/SLAMS network and CMAQ numerical output, specifically, 24h $PM_{2.5}$ concentrations at 12x12km grid cells simulated using CMAQ version 4.6 (Holland 2012). CMAQ is a

sophisticated and extensively reviewed (Aiyyer et al. 2007; Amar et al. 2004; Amar et al. 2005) regional air quality model that estimates pollutant concentrations and deposition fluxes at local, regional, and continental scales. Using meteorological and emissions data, CMAQ simulates pollutant transformation, transport, and fate. Meteorological variables were estimated using 5th generation Mesoscale Model version 3.6.3. The emissions inventory was based on the 2002 National Emissions Inventory and daily continuous emissions monitoring data for major point sources of nitrogen oxides (Holland 2012).

The downscaler uses monitoring data and gridded CMAQ output (12x12km) to estimate daily air pollution concentrations at census tract centroids using linear regression modeling with additive and multiplicative bias coefficients that can vary spatially and temporally (Berrocal et al. 2012; Berrocal et al. 2010a, b). Downscaler estimates are used in EPA's Environmental Justice mapping and screening tool (EJSCREEN) (U.S. EPA 2015) and studies of air pollution and health (Gray et al. 2014). Although the downscaler was developed to provide predictive surfaces of air pollution for health studies relating daily pollution levels to daily health outcomes (Holland 2012), downscaler performance in locations without monitoring data, which correspond primarily to less urban areas, is not well characterized. Thus, use of downscaler output allows us to estimate exposures and health effects in nonurban locations, but resulting health effect estimates should be interpreted with care, as there may be significant differences in downscaler performance in urban vs. less urban locations.

We use downscaler output consisting of daily $PM_{2.5}$ concentration estimates at census tracts for the eastern two-thirds of the US, the region for which downscaler output are available for 2002-2006 (Figure 1). Further details on the downscaler methodology, results, and validation are available elsewhere (Berrocal et al. 2012).

We generated 24h county-level $PM_{2.5}$ estimates using multiple approaches. We only estimated exposures for counties with population ≥50,000 (n=795) to ensure sufficient sample size. First, we used the standard approach of estimating exposures from monitoring data for counties with monitors (n=446) and days with observations. Approximately 80% of $PM_{2.5}$ monitors record observations once every three days. Multiple monitor measurements for the same day and county were averaged. Second, county-level 24h $PM_{2.5}$ exposures were calculated from a population-weighted average of $PM_{2.5}$ concentrations predicted by the downscaler at census tracts within each county using 2000 Census data (U.S. Census Bureau 2000a). These exposure estimates, heretofore referred to as "CMAQds," were generated for 795 counties in the study area with a population ≥50,000 and all days in the study period (2002-2006). Lastly, we subset the CMAQds dataset and calculated population-weighted county-level exposures *only* for counties and days with monitoring data. The dataset of county-level $PM_{2.5}$ exposures derived from downscaler output but restricted to days and counties with monitoring data is referred to as "CMAQds_subset."

Thus, we have three datasets of county-level exposure estimates, derived from: (1) $PM_{2.5}$ monitoring data; (2) all available downscaler output (CMAQds); and (3) downscaler output only in counties and on days with monitoring data (CMAQds_subset). Attributes of each $PM_{2.5}$ dataset and methods used to estimate exposures are summarized in the Supplemental Material (SM), Table S1. We assessed whether monitor and downscaler-derived exposure estimates were similar using metrics from the literature (Zhang et al. 2006).

Counties were divided into five urbanicity categories based on percent of the county population residing in urban settings. According to the census, urban populations reside in census blocks with (1) population density of ≥1,000 people/square mile (mi^2) and (2)

surrounding census blocks with density of ≥500 people/mi^2; rural populations reside in blocks that do not meet these criteria (U.S. Census Bureau 2000b). Urban/rural categories are mutually exclusive, i.e., 100 less the percentage of the population residing in urban areas equals the percentage of the population residing in rural areas. The five categories of urbanicity consisted of counties with >90%, 81-90%, 61-80%, 41-60%, and ≤40% of the population residing in urban settings. The percent of population in urban and rural (referred to here as "nonurban") settings was obtained from the 2000 Census Summary File 3 (U.S. Census Bureau 2000a).

Daily temperature and dew point temperature data were obtained from the National Climatic Data Center (National Climatic Data Center 2012). Daily, 24h estimates of temperature and dew point temperature for each county were generated from observations from all weather stations within the county. If a county did not have a weather monitor, weather data from the closest county within 30 miles was used. Counties with insufficient meteorological data (n=87) were removed from analysis. This restriction resulted in 418 counties in the monitor and CMAQds_subset exposure datasets, and 708 counties in the CMAQds exposure dataset.

Statistical analysis

Health effects were estimated using two-stage Bayesian hierarchical modeling, an approach described elsewhere (Bell et al. 2004). In the first stage, log-linear Poisson regression models with over-dispersion were fit to county-specific time-series data on hospital admission rates and $PM_{2.5}$ concentrations, adjusted for covariates. We chose covariates based on previous analyses (Dominici et al. 2006). Covariates included smooth functions (natural cubic spline) of same-day (day 0) temperature and dew point temperature [degrees of freedom (df) = 6], 3-day moving average of temperature and dew point temperature for days 1-3 (df = 3), and time to account for long-term trends in hospitalizations (df = 8/year), as well as categorical variables for

age (65–74y, >74y) and day of week. The age variable was included to account for differential effects of air pollution by age, as done in earlier studies (Bell et al. 2008). Lags for temperature and dew point temperature were consistent across all analyses.

In the second stage, we estimated the short-term association between $PM_{2.5}$ and hospital admissions for the entire study area using two-level normal independent sampling estimation with non-informative priors (Everson and Morris 2000). This allows us to combine relative risk estimates across counties while accounting for within-county statistical error and between-county variability in the true relative risks. The result is an overall effect estimate of the relationship between $PM_{2.5}$ and hospital admissions across all counties. Alternatively, we can estimate the relationship between $PM_{2.5}$ and hospitalizations for selected groups of counties that share characteristic(s) of interest, such as degree of urbanicity. Each hospitalization type (cardiovascular or respiratory) and $PM_{2.5}$ dataset (CMAQds, CMAQds_subset, or monitor-based estimates) was analyzed separately. County-level and overall (combined) effects were estimated for cardiovascular outcomes and respiratory outcomes at lag 0, lag 1 (previous day exposure), and lag 2. Effect estimates were compared to determine if they were significantly different based on Schenker and Gentleman (2001).

To investigate whether $PM_{2.5}$-hospitalization associations differ for single or multiple days of exposure, we fit a distributed lag model with multiple lags of pollution (0 to 7 day lags) simultaneously included in the county-specific model. We then investigated whether effect estimates differed for more versus less urban counties using CMAQds-derived exposures, performing analysis stratified by the five urbanicity categories discussed previously

Results are presented as the estimated percent increase in hospital admissions associated with a $10\mu g/m^3$ increase in $PM_{2.5}$ across a specified number of days. Statistical significance was

assessed by the 95% posterior intervals (PI) excluding the value of zero. Statistical analyses were performed using R version 3.2.1 (R Development Core Team 2014), and using the package tlnise for two-level normal independent sampling.

RESULTS

Observed concentrations are compared to CMAQds predictions in SM, Table S2; see SM, Figure S1 for a map of monitoring data availability by county. Mean daily county-level concentrations derived from monitoring data and CMAQds_subset were 12.48 $\mu g/m^3$ and 12.60 $\mu g/m^3$, respectively. Mean and median within-county correlation between monitored and CMAQds_subset-predicted county-level concentrations were 0.96 and 0.97, respectively (std. deviation = 0.032; minimum and maximum = 0.72 and 0.99, respectively) (see SM, Figure S2). Average normalized mean bias was <1%, indicating that systematic bias in CMAQds_subset-predicted county-level $PM_{2.5}$ concentrations was low.

$PM_{2.5}$-hospitalization associations were estimated using exposures derived from: (1) monitoring data (n=418 counties); (2) CMAQds_subset (n=418 counties); and (3) CMAQds (n=708 counties). County-specific maximum likelihood effect estimates resulting from the first stage model using monitor- and CMAQds-derived exposure estimates are summarized in SM, Figure S3. Overall estimates of cardiovascular and respiratory associations using different exposure datasets were similar (Table 1): based on CMAQds-derived exposure estimates, a $10\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 1.16% [95% confidence interval: 0.88%-1.45%] increase in same day (lag 0) respiratory admissions and a 0.79% (0.62%, 0.97%) increase in same day cardiovascular admissions. Using CMAQds-derived exposure estimates, positive, statistically significant associations were observed for cardiovascular hospitalizations at lag 0 and for respiratory hospitalizations at lag 0, lag 1, and lag 2 (Table 1). Effect estimates from the

different exposure datasets at the single lags examined (lag 0, 1, and 2) were similar in magnitude and not significantly different from one another. For respiratory hospitalizations, lag 0 effect estimates tended to be larger than lag 1 or lag 2 effects, regardless of the exposure estimates used. Cardiovascular effect estimates at lag 2 were negative when CMAQds_subset exposures were used (-0.20% [-0.43%, 0.03%]).

Daily CMAQds-derived exposure estimates allow investigation of short-term cumulative lag effects. We used daily CMAQds-derived exposure estimates to include multiple single-day lags of $PM_{2.5}$ concentration simultaneously in a distributed lag model, allowing pollution over multiple previous days to influence health (Peng and Dominci 2008). Health effects estimated for up to seven days of multi-day lags (lag 01 through 07) using CMAQds-derived exposure estimates are presented in Figure 2. Point estimates for cardiovascular admissions decrease as more days are included in the lag structure, but remain similar (range: 0.65% to 0.89% increase in admissions per 10μg/m^3 $PM_{2.5}$ increase). Associations for respiratory hospitalizations are positive and statistically significant from lag 01 to lag 06, and effect estimates increase with additional days included in the lag through lag 07. The largest association was observed for lag 01 (0.89% [0.51%-1.28%]) for cardiovascular admissions and lag 06 (2.47% [0.29%-4.69%]) for respiratory admissions. Sensitivity analysis indicated that larger $PM_{2.5}$ effects for respiratory outcomes at longer lag times were not attributed to uncontrolled temperature effects at longer lags. Lag results should be interpreted with caution: CMAQds-derived estimates may have greater day-to-day correlation than monitoring data, as emissions inputs to CMAQ are correlated across time.

For the urbanicity analysis, we divided counties into five groups based on the percentage of county population residing in urban areas. Of 708 counties, 153 had >90% of the population

residing in urban settings (median population density = 477 people/square kilometer [km^2]), 113 counties had 81-90% of the population in urban areas (139 people/km^2), 235 counties had 61-80% of the population in urban areas (78 people/km^2), 140 counties had 41-60% of the population in urban settings (50 people/km^2), and 67 counties had ≤40% of the population in urban settings (34 people/km^2) (Figure 1). Mean $PM_{2.5}$ for each of the urbanicity groups was not significantly different (t-test with Welch correction for unequal variances). Counties with >90% or 61-80% of the population residing in urban areas had the highest average $PM_{2.5}$ concentrations (12.5 μg/m^3), while counties with ≤40% of the population residing in urban areas had the lowest concentration (11.8 μg/m^3). The standard error of $PM_{2.5}$ concentrations associated with downscaler predictions did not differ substantially by urbanicity (results not shown). Average (minimum-maximum) counts of daily, county-level cardiovascular-related hospitalizations ranged from 1.88 (0-15) in the most nonurban counties to 13.8 (0-224) in the most urban counties. For respiratory hospitalizations, average (minimum-maximum) counts of daily, county-level hospitalizations ranged from 0.73 (0-10) in the most nonurban counties to 4.44 (0-153) in the most urban counties.

Figure 3 shows health effect estimates by urbanicity category (lag 0), estimated using CMAQds exposure estimates. Cardiovascular effect estimates increase with increasing urbanicity. In contrast, the largest effect for respiratory hospitalizations (2.57% [0.87%-4.30%] for a 10μg/m^3 increase in lag 0 $PM_{2.5}$), is observed in counties with ≤40% of population in urban areas. We also observed positive, statistically significant respiratory associations in some of the more urban populations. Findings indicate that cardiovascular effects are higher in the most urban counties, while respiratory effects are highest in the least urban counties. However, respiratory and cardiovascular effect estimates for counties with differing levels of urbanicity

were not significantly different. We considered alternative groupings of urbanicity, and found that categorizing urbanicity using four or five levels gave very similar results (results not shown). Health effect estimates by urbanicity estimated only for counties with monitoring data are provided in SM, Figure S4.

DISCUSSION

Our principal findings are: (1) evidence that $PM_{2.5}$ may exert higher cardiovascular risk in urban populations; (2) suggestive evidence that $PM_{2.5}$ is more detrimental to respiratory health in nonurban populations; and (3) evidence that respiratory health, more so than cardiovascular health, is affected by $PM_{2.5}$ over the past few days. Our findings with respect to urban populations are consistent with those of previous studies focusing primarily on urban populations, which observed associations between short-term $PM_{2.5}$ exposure and cardio-respiratory health, e.g., (Dominici et al. 2006; Krall et al. 2013; Samet et al. 2000; Zanobetti et al. 2009). However, our findings also indicate that estimating risks using monitor data alone may underestimate the true effect across urban and nonurban populations, which occurs at a lag of a week (or longer) for respiratory hospitalizations.

Scientific evidence on urban and nonurban differences in $PM_{2.5}$ composition is extremely limited (Kelly and Russell 2012), in part due to the dearth of monitors in less urban areas. An analysis of hospitalizations and satellite-derived $PM_{2.5}$ estimates in the Mid-Atlantic US found differences in associations between $PM_{2.5}$ and cardiovascular hospitalizations in urban and rural populations (Kloog et al. 2014); others observed associations between respiratory health and urbanization (Ebisu et al. 2011). The urban-nonurban discrepancies in health response we observed could result from multiple factors, such as differences in exposure to pollutant mixtures

(e.g., source-dependent $PM_{2.5}$ composition), susceptibility to a given exposure in each population (e.g., due to baseline health status, access to or quality of health care, co-exposures, co-morbidities), and exposure measurement error.

Increasingly, evidence indicates that PM toxicity relates to chemical composition (Krall et al. 2013; Lippman et al. 2006) and source (Kelly and Russell 2012). $PM_{2.5}$ chemical composition varies by geography, source, and season (Bell et al. 2007): pollutant mixtures, and associated toxicity, may differ by urbanicity (Schwab et al. 2004), which could affect observed associations. This could explain our findings that urban/nonurban differences in associations vary by cause of hospital admission, as various chemical structures may affect health through different physiological pathways.

Urban and nonurban populations may have differential susceptibility to a given level of air pollution exposure ("effect modification") (Greenland and Morgenstern 1989), which could relate to health care, lifestyle, activity patterns, and co-morbidities or risk factors. Compared to urban areas, nonurban areas have higher poverty levels (The Housing Assistance Council 2011); fewer physicians per capita; and greater transportation barriers to health care (Eberhardt et al. 2001; Vanasse et al. 2010). Distributions of co-morbidities or risk factors in urban and nonurban populations may play a role in susceptibility to $PM_{2.5}$. For example, a study of diabetes and coronary heart disease indicated that disease prevalence rates were higher in nonurban areas, but after adjusting for risk factors (e.g., poverty, obesity, tobacco use), prevalence was lower among respondents in nonurban areas compared to urban areas (O'Connor and Wellenius 2012). Lifestyle factors and activity patterns may also play a role: compared to nonurban residents, urban residents are more likely to engage in physical activity (Parks et al. 2003). Research in

Canada found that rural populations spent significantly more time working outdoors (Matz et al. 2015). Such differences may affect not only susceptibility, but exposures levels.

Exposure measurement error may also contribute to differences in effect estimates for urban and nonurban counties. One key challenge is that evaluation of exposure estimates through comparison to monitoring data is limited in nonurban areas due to the lack of monitors. Validation of downscaler $PM_{2.5}$ concentrations is only possible in locations with monitoring data; thus, it is not possible to evaluate downscaler performance in counties without ambient monitors, which tend to be less urban. However, less urban areas are the very locations where exposure estimates are most needed. Zeger et al. (2000) identify three components of measurement error: (1) difference between individual exposures and average personal exposure; (2) difference between average personal exposure and ambient levels; and (3) difference between measured and true ambient concentrations. The difference between downscaler-predicted and measured ambient concentrations is particularly relevant to our study. The downscaler incorporates information from ambient monitors, which are generally located in more urban settings, such that exposure estimates may have less measurement error in more urban areas. One study of exposure measurement error in a time-series context such as ours indicated that larger differences between measured and true concentrations resulted in attenuated estimates of health risk (Goldman et al. 2011). However, depending on the error type (e.g., classical, Berkson), risk ratios could be attenuated or biased away from the null. Other issues (e.g., chemical composition, co-morbidities) may be as or more important than measurement error.

Another principal finding is the lag structures observed for $PM_{2.5}$ exposure and impacts on respiratory and cardiovascular hospitalizations. We found that the largest impact of $PM_{2.5}$ on cardiovascular hospitalizations occurred at short lag time of 0-1 days, while the largest impact on

respiratory hospitalizations occurred at a lag of a week (Figure 2). This is consistent with an earlier study of PM_{10} (Zanobetti et al. 2003), in which risk of respiratory mortality increased five-fold when PM_{10} exposure was characterized by longer distributed lags. Our findings with respect to lags are also consistent with several city-specific investigations that use daily air pollution data to evaluate lags between $PM_{2.5}$ and cardiovascular- and respiratory-related morbidity and mortality, including studies in Denver, Seattle (Kim et al. 2012), and Detroit (Zhou et al. 2011), among others (Schwartz 2000). This is a critical point because it is not possible to estimate health impacts of short-term cumulative exposures in most US locations using traditional methods, as very few monitors measure $PM_{2.5}$ daily: of 708 counties in this analysis, just 57 (8.1%) had >90% of days with monitoring data. As a result, any analysis of cumulative exposures using monitoring data is necessarily constrained to areas with daily monitoring data, which are overwhelmingly urban.

Moreover, our analysis indicated that counties for which short-term cumulative exposure and health effects could be estimated using monitor-derived exposures (i.e., primarily urban counties with daily data), have lower effect estimates for respiratory hospitalizations compared to other counties (i.e., those with less $PM_{2.5}$ monitoring data availability) (results not shown). Thus, respiratory health effects modeled using distributed lag exposures obtained from counties with near-complete monitoring data may not be generalizable to counties with little or no monitoring data, and may in fact underestimate health effects in such counties.

Our study has several limitations. Analysis was restricted to counties with populations $\geq$50,000 in the 2000 Census, which limits how nonurban included counties can be, since more sparsely populated rural counties often have populations <50,000. This analytical design was chosen for sample size considerations, and our findings indicate that further investigation of

health impacts of air pollution in nonurban populations is warranted. Although we evaluated CMAQds performance with respect to monitoring data, CMAQds performance cannot be evaluated in areas with limited or no monitoring data. Differences between CMAQds-derived exposure estimates and monitor-derived exposure estimates may be greater in less urban counties because there is little or no monitoring data to use as input to the downscaler in less urban areas. Clearly there is less opportunity to validate CMAQds-derived exposure estimates in places without monitors, the very places where exposure estimates are most needed. The potential difference in error between urban and less urban counties means that differences in risk estimates for urban and less urban counties must be interpreted with caution, and this is an area in which the need for further research is acute. We do not have substantial data on spatial variability or urban/nonurban differences in $PM_{2.5}$ composition or co-pollutant concentrations or mixtures. Additionally, although the ≥65y demographic is one of the fastest growing segments of the US population (Ortman et al. 2014), and older individuals may have heightened susceptibility to air pollution (Sacks et al. 2011), health effects estimated for elderly individuals are not necessarily generalizable to the US population or other potentially susceptible populations. This study was limited to areas were CMAQds-predicted concentrations were available for 2002-2006.

Strengths of this study include the investigation of several important questions that are not addressed in previous studies, including health effect estimates in nonurban counties, since monitors tend to be sited in urban locations, and health effects of short-term cumulative exposures (distributed lags). A major strength of this study is inclusion of understudied populations residing in nonurban areas; previous multi-city studies of air pollution have been based exclusively in more urban counties and communities, and city-specific studies also tend to focus on metropolitan areas (Zanobetti and Schwartz 2005). Another significant strength is our

analysis of short-term distributed lags in areas with non-daily monitoring data or no data. Future work could incorporate uncertainty associated with downscaler predictions into the exposure and health effect estimates, investigate whether results are affected by co-morbidities, lifestyle, or risk factors that may affect susceptibility to air pollution or cardiovascular or respiratory disease, and examine even more rural counties by pooling populations in adjacent counties or similar methods.

CONCLUSION

As a result of urban bias in epidemiological studies, which is largely driven by data availability, the health impacts of air pollution in nonurban locations are largely unknown. Health effect estimates for predominantly urban populations may not be generalizable to nonurban areas, where over 59 million people live in the US. Further, estimating health effects of $PM_{2.5}$ with non-daily data may underestimate true health effects, particularly for respiratory-related hospitalizations. Health analyses in urban locations, with high populations and pollution levels, are useful from public health impact and regulatory perspectives; however, health outcomes for large numbers of people remain poorly understood. Our findings point to significant respiratory health impacts in nonurban areas and over a multi-day exposure period. Additional research is needed to investigate health impacts of air pollution on nonurban populations and to explore the differences in health effect estimates presented here.

6. References

Aiyyer A, Cohan D, Russell AG, Stockwell W, Tanrikulu S, Vizuete W, et al. 2007. Final Report: Third Peer Review of the CMAQ Model. University of North Carolina, Chapel Hill, NC.

Amar P, Chock D, Hansen M, Moran A, Steyn R, Stockwell W. 2005. Final Report: Second Peer Review of the CMAQ Model. University of North Carolina, Chapel Hill, NC.

Amar P, Bornstein H, Feldman H, Jeffries D, Steyn R, YZhang Y. 2004. Final Report: December 2003 Peer Review of the CMAQ Model. University of North Carolina, Chapel Hill, NC.

Bell ML, Ebisu K, Peng RD, Walker J, Samet JM, Zeger SL, et al. 2008. Seasonal and regional short-term effects of fine particles on hospital admissions in 202 U.S. counties, 1999-2005. Am Journ Epidemiol 168(11): 1301-1310.

Bell ML, Dominci F, Ebisu K, Zeger SL, Samet JM. 2007. Spatial and temporal variation in $PM_{2.5}$ chemical composition in the United States for health effect studies. Environ Health Perspect 115(7): 989-995.

Bell ML, McDermott A, Zeger SL, Samet JM, Dominici F. 2004. Ozone and short-term mortality in 95 U.S. urban communities, 1987-2000. J Am Med Assoc 292(19): 2372-2378.

Berrocal V, Gelfand AE, Holland DM. 2012. Space-time data fusion under error in computer model output: An application to modeling air quality. Biometrics 68(3): 837-848.

Berrocal VJ, Gelfland AE, Holland DM. 2010a. A Spatio-Temporal Downscaler for Output from Numerical Models. Journal of Agricultural, Biological, and Environmental Statistics 15(2): 176-197.

Berrocal VJ, Gelfland AE, Holland DM. 2010b. A bivariate space-time downscaler under space and time misalignment. Annals of Applied Statistics 4(4): 1942-1975.

Bravo MA, Fuentes M, Zhang Y, Burr M, Bell ML. 2012. Comparison of exposure estimation methods for ambient air pollutants: Ambient monitoring data and regional air quality simulation. Environ Res 116: 1-10.

Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, et al. 2006. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. J Am Med Assoc 295(10): 1127-1134.

Dominici F, McDermott A, Zeger SL, Samet JM. 2003. National maps of the effects of particulate matter on mortality: Exploring geographical variation. Environ Health Perspect 111: 39-42.

Eberhardt MS, Pamuk ER. 2004. The importance of place of residence: examining health in rural and nonrural areas. Am J Public Health 94(10): 1682-1686.

Eberhardt MS, Ingram DD, Makuc DM. 2001. Urban and Rural Health Chartbook. Hyattsville, Maryland:National Center for Health Statistics.

Ebisu K, Holford TR, Belanger KD, Leaderer BP, Bell ML. 2011. Urban land-use and respiratory symptoms in infants. Environ Res 111(5): 677-684.

Everson PJ, Morris CN. 2000. Inference for multivariate normal hierarchical models. J Roy Stat Assoc B 62: 399-412.

Goldman GT, Mulholland JA, Russell AG, Strickland MJ, Klein M, Waller LA, et al. 2011. Impact of exposure measurement error in air pollution epidemiology: effect of error type in time series studies. Environmental Health 10(61).

Gray SC, Edwards SE, Schultz BD, Miranda ML. 2014. Assessing the impact of race, social factors and air pollution on birth outcomes: a population-based study. Environmental Health 13(4).

Greenland S, Morgenstern H. 1989. Ecological Bias, Confounding, and Effect Modification. Int J Epi 18(1): 269-274.

Hartley D. 2004. Rural health disparities, population health, and rural culture. Am J Public Health 94(10): 1675-1680.

Hyder A, Lee HJ, Ebisu K, Koutrakis P, Belanger K, Bell ML. 2014. $PM_{2.5}$ exposure and birth outcomes: Use of satellite- and monitor-based data. Epidemiology 25(1): 58-67.

Kelly FJ, Russell JC. 2012. Size, source, and chemical composition as determinants of toxicity attribuatble to ambient particulate matter. Atmos Environ 60: 504-426.

Kim S-Y, Peel JL, Hannigan MP, Dutton SJ, Sheppard L, Clark ML, et al. 2012. The Temporal Lag Structure of Short-term Associations of Fine Particulate Matter Chemical Constituents and Cardiovascular and Respiratory Hospitalizations. Environ Health Perspect 120(8): 1094-1099.

Kloog I, Nordio F, Zanobetti A, Coull BA, Schwartz JD. 2014. Short term effects of particle exposure on hospital admissions in the Mid-Atlantic states: a population estimate. PLoS One 9(2).

Kloog I, Koutrakis P, Coull BA, Lee HJ, Schwartz J. 2011. Assessing temporally and spatially resolved $PM_{2.5}$ exposures for epidemiological studies using satellite aerosol optical depth measurements. Atmos Environ 45(35): 6267-6275.

Krall JR, Anderson GB, Dominici F, Bell ML, Peng RD. 2013. Short-term exposure to particulate matter constituents and mortality in a national study of U.S. urban communities. Environ Health Perspect 121(10): 1148-1153.

Lee M, Kloog I, Chudnovsky A, Lyapustin A, Wang Y, Melly S, et al. 2015. Spatiotemporal prediction of fine particulate matter using high-resoluation satellite images in the Southeastern US, 2003-2011. J Expo Sci Environ Epi 2015.

Lippman M, Ito K, Hwang JS, Maciejczyk P, Chen LC. 2006. Cardiovascular effects of nickel in ambient air. Environ Health Perspect 114(11): 1662-1669.

Matz CJ, Stieb DM, Brion O. 2015. Urban-rural differences in daily time-activity patterns, occupational activity, and housing characteristics. Environmental Health 14(88).

Holland D. 2012. Fused Air Quality Predictions Using Downscaling Research Triangle Park, NC.

Miranda ML, Edwards SE, Keating MH, Paul CJ. 2011. Making the Environmental Justice Grade: The Relative Burden of Air Pollution Exposure in the United States. Int J Environ Res Public Health 8: 1755-1771.

National Climatic Data Center. 2012. U.S. Local Climatological Data. NCDC Daily Surface Data. Asheville, NC.

O'Connor A, Wellenius GA. 2012. Rural-urban disparities in the prevalence of diabetes and coronary heart disease. Public Health 126(10): 813-820.

Ortman JM, Velkoff VA, Hogan H. 2014. An Aging Nation: The Older Population in the United States. Washington, D.C. U.S. Department of Commerce, Economics and Statistics Administration.

Parks SE, Housemann RA, Brownson RC. 2003. Differential correlates of physical activity in urban and rural adults of various socioeconomic backgrounds in the United States. J Epidemiol Commun H 57(1): 29-36.

Peng RD, Dominci F. 2008. Statistical Methods for Environmental Epidemiology with R: A Case Study of Air Pollution and Health. Baltimore, MD: Springer.

Peng RD, Dominci F, Pastor-Barriuso R, Zeger SL, Samet JM. 2005. Seasonal analyses of air pollution and mortality in 100 U.S. cities. Am Journ Epidemiol 161: 585-594.

R Development Core Team. 2014. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing.

Sacks JD, Stanek LW, Luben TJ, Johns DO, Buckley BJ, Brown JS, et al. 2011. Particulate Matter–Induced Health Effects: Who Is Susceptible? Environ Health Perspect 119: 446-454.

Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. 2000. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med 343(24): 1742-1749.

Schenker N, Gentleman J. 2001. On Judging the Signifiance of Differencves by Examining the Overlap Between Confidence Intervals. The American Statistician 55(3):182-186.

Schwab JJ, Felton HD, Demerjian KL. 2004. Aerosol chemical composition in New York state from integrated filter samples: Urban/rural and seasonal contrasts. Journal of Geophysical Research:Atmosphere 109(D16).

Schwartz J. 2000. The distributed lag between air pollution and daily deaths. Epidemiology 11(3): 320-326.

The Housing Assistance Council. 2011. Poverty in Rural America. Washington, D.C. The Housing Asssitance Council.

U.S. Census Bureau. 2000a. Census 2000 Summary File 3. (U.S. Department of Commerce, ed). Washington, D.C.

U.S. Census Bureau. 2000b. Census 2000 Urban and Rural Classification. Available: https://www.census.gov/geo/reference/ua/urban-rural-2000.html.

U.S. Environmental Protection Agency. 2015. EJSCREEN: Environmental Justice Mapping and Screening Tool Technical Documentation. Washington, D.C. U.S. EPA Office of Policy.

Vanasse A, Courteau J, Cohen AA, Orzanco MG, Drouin C. 2010. Rural-urban disparities in the management and health issues of chronic diseases in Quebec (Canada) in the early 2000s. Rural Remote Health 10(4).

Zanobetti A, Franklin M, Koutrakis P, Schwartz J. 2009. Fine particulate air pollution and its components in association with cause-specific emergency admissions. Environmental Health 8(58).

Zanobetti A, Schwartz J. 2005. The Effect of Particulate Air Pollution on Emergency Admissions for Myocardial Infarction: A Multicity Case-Crossover Analysis. Environ Health Perspect 113(8): 978-982.

Zanobetti A, Schwartz J, Samoli E, Gryparis A, Touloumi G, Peacock J, et al. 2003. The temporal pattern of respiratory and heart disease mortality in response to air pollution. Environ Health Perspect 111(9): 1188-1193.

Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery DW, Cohen A. 2000. Exposure measurement error in time-series studies of air pollution: Concepts and consequences. Environ Health Perspect 108(5):419-426.

Zhang Y, Liu P, Pun B, Seigneur C. 2006. A comprehensive performance evaluation of MM5-CMAQ for the Summer 1999 Southern Oxidants Study episode - Part I: Evaluation protocols, databases, and meteorological predictions. Atmos Environ 40: 4825-4838.

Zhou J, Ito K, Lall R, Lippmann M, Thurston G. 2011. Time-series analysis of mortality effects of fine particulate matter components in Detroit and Seattle. Environ Health Perspect 119: 461-466.

Table 1. Percent Increase in Hospital Admissions Associated with a 10μg/m^3 Increase in $PM_{2.5}$ Concentration, 2002-2006*

Health effect	Monitor data (n=418 counties)		CMAQds_subset (n=418 counties)		CMAQds (n=708 counties)	
	Estimate	95% PI	Estimate	95% PI	Estimate	95% PI
Cardiovascular						
lag 0	**0.87**	**0.65, 1.09**	**0.98**	**0.73, 1.23**	**0.79**	**0.62, 0.97**
lag 1	0.15	-0.06, 0.37	0.15	-0.09, 0.38	-0.004	-0.16, 0.15
lag 2	-0.14	-0.36, 0.07	**-0.20**	**-0.43, -0.03**	0.09	-0.06, 0.24
Respiratory						
lag 0	**1.10**	**0.70, 1.50**	**1.11**	**0.66, 1.56**	**1.16**	**0.88, 1.45**
lag 1	**0.37**	**0.01, 0.78**	0.38	-0.02, 0.80	**0.29**	**0.015, 0.58**
lag 2	**0.57**	**0.22, 0.93**	**0.57**	**0.18, 0.96**	**0.37**	**0.11, 0.63**

*Values in bold are statistically significant $p<0.05$.

Figure Legends

Figure 1. Percent of county population residing in urban areas. Urban populations reside in census blocks with population density of ≥1,000 people/square mile (mi^2) and (2) surrounding blocks with a density of ≥500 people/mi^2. Rural populations are any population located outside of urban census blocks (U.S. Census Bureau 2000b). Shading indicates which counties were included in the study (n=708 counties), with dark gray representing the most urban counties and light gray representing the most rural counties. Counties with the highest levels of urbanicity (>90% of county population residing in urban settings) primarily correspond to counties containing or surrounding the following major cities: Houston, San Antonio, Austin, Odessa, Laredo, Brownsville, Corpus Christie, El Paso, and Dallas/Fort Worth, TX; Albuquerque, NM; Denver, Aurora, and Colorado Springs, CO; Omaha and Lincoln, NE; Tulsa and Oklahoma City, OK; Wichita and Kansas City, KS; Minneapolis-St. Paul, MN; Milwaukee, WI; Chicago, IL; St. Louis, MO; Fort Wayne and Indianapolis, IN; Detroit, MI; Buffalo and Schenectady, NY; Pittsburgh, PA; Nashville and Memphis, TN; Louisville and Lexington, KY; Cincinnati, Cleveland, Columbus, and Toledo, OH; Washington, DC; Norfolk, VA; Charlotte, Greensboro, and Raleigh, NC; Atlanta, Georgia; New Orleans and Baton Rouge, LA; and Tampa, Orlando, Miami, and Jacksonville, FL. There is a corridor of high urbanicity counties along the eastern seaboard, extending roughly from Baltimore, MD to Boston, MA. The most urban counties are often bordered, at least in part, by other counties with middling to high levels of urbanicity (e.g., 41-90% of county population residing in urban settings). More rural counties are more common in interior (i.e., non-coastal) areas of the southeast, including Oklahoma; the Northeast; the Ohio River Valley; and Midwest. Ambient $PM_{2.5}$ monitors are more likely to be sited in areas with higher levels of urbanicity.
County boundaries are drawn according to Census 2000 Topologically Integrated Geographic Encoding and Referencing (TIGER)/Line files.

Figure 2. Percent increase in hospital admissions associated with a 10μg/m^3 increase in $PM_{2.5}$ concentration, estimated for short-term distributed lags, using CMAQds exposure estimates. Vertical lines represent 95% posterior intervals.

Figure 3. Percent increase in hospital admissions associated with a 10μg/m^3 increase in $PM_{2.5}$ concentration, estimated for counties with different levels of urbanicity (lag 0). Vertical lines represent 95% posterior intervals.

Figure 1.

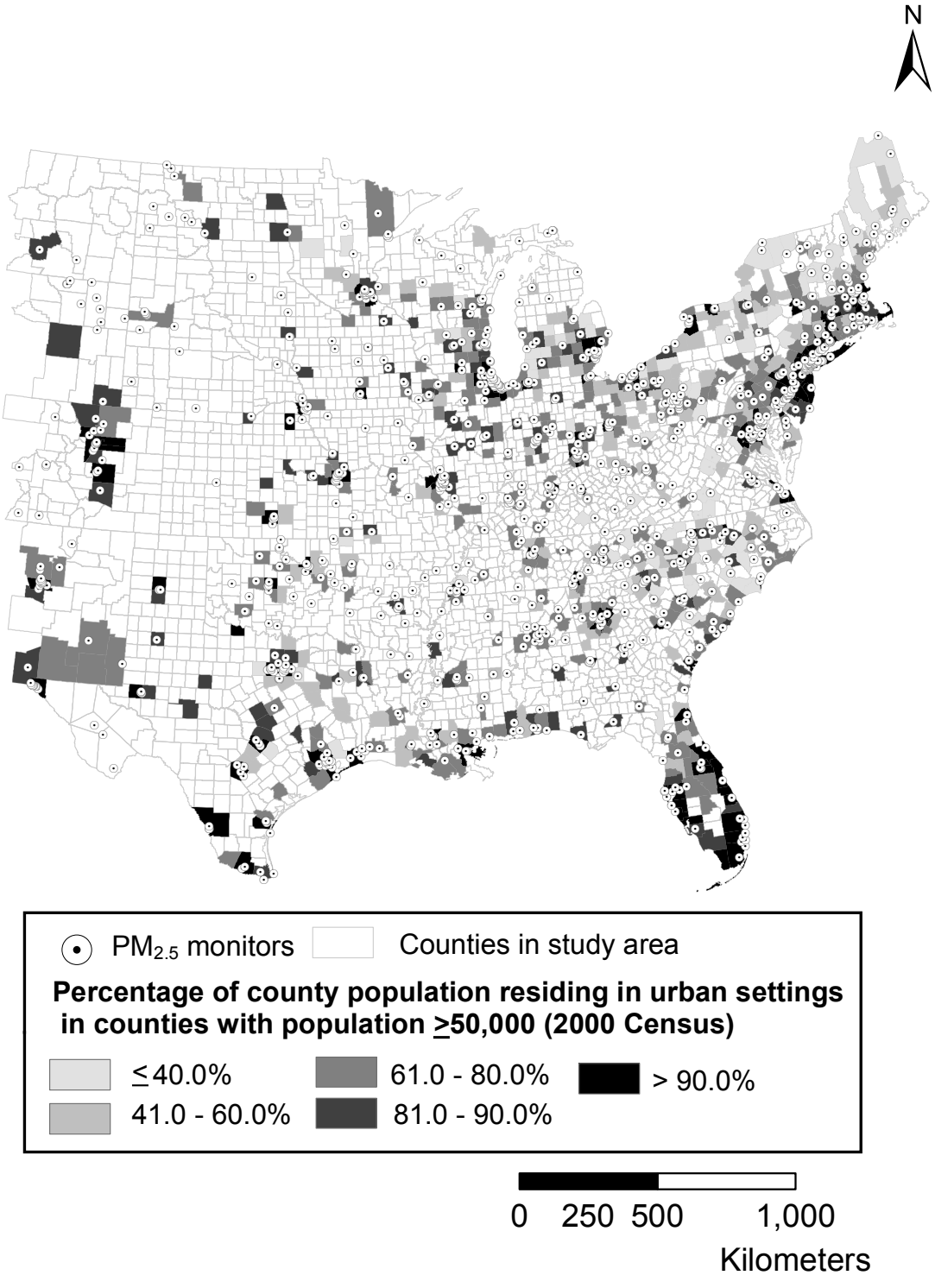

N
PM2.5 monitors
Counties in study area
Percentage of county population residing in urban settings in counties with population ≥50,000 (2000 Census)
≤40.0%
41.0 - 60.0%
61.0 - 80.0%
81.0 - 90.0%
> 90.0%
0 250 500 1,000
Kilometers

Figure 2.

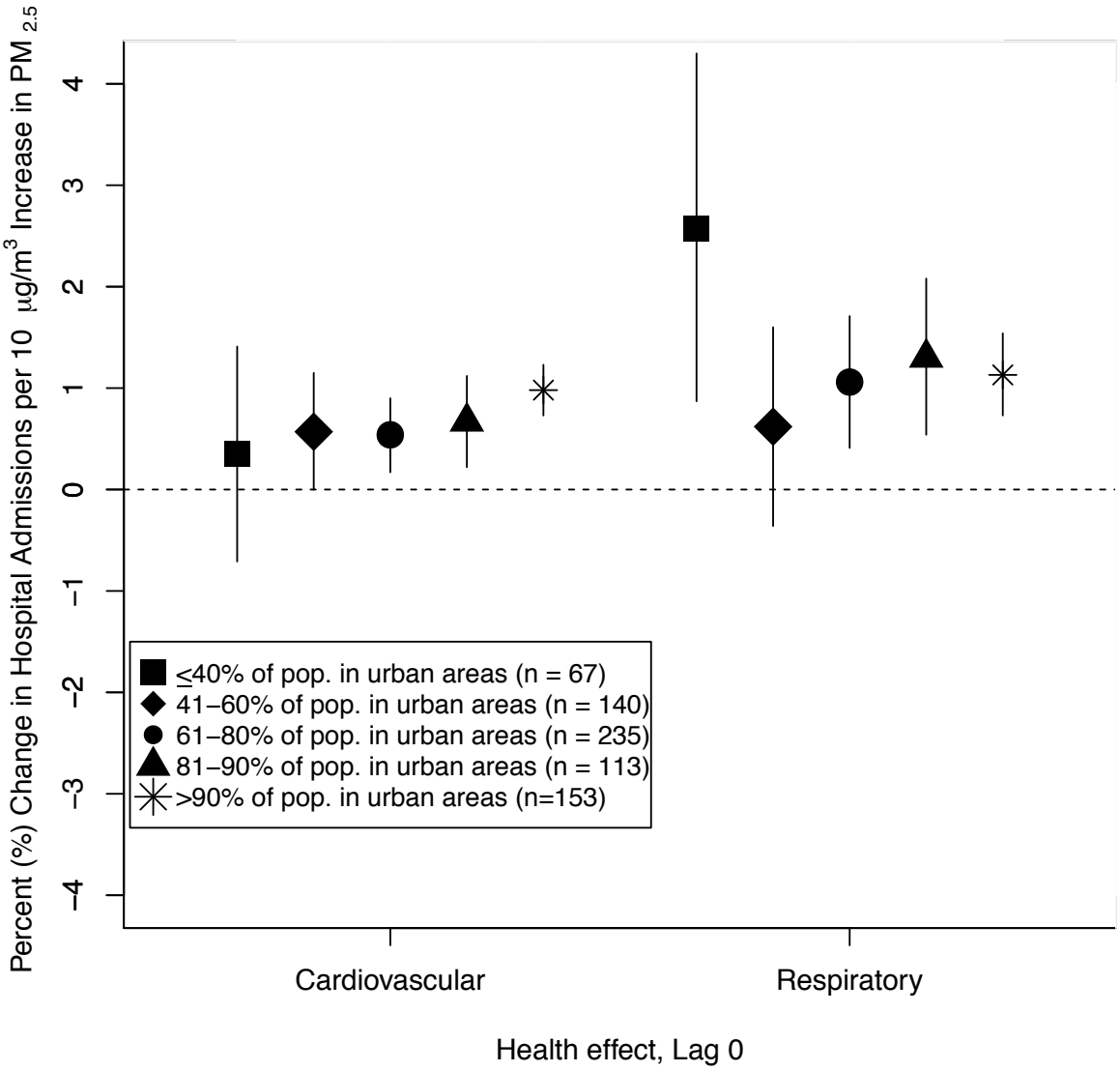
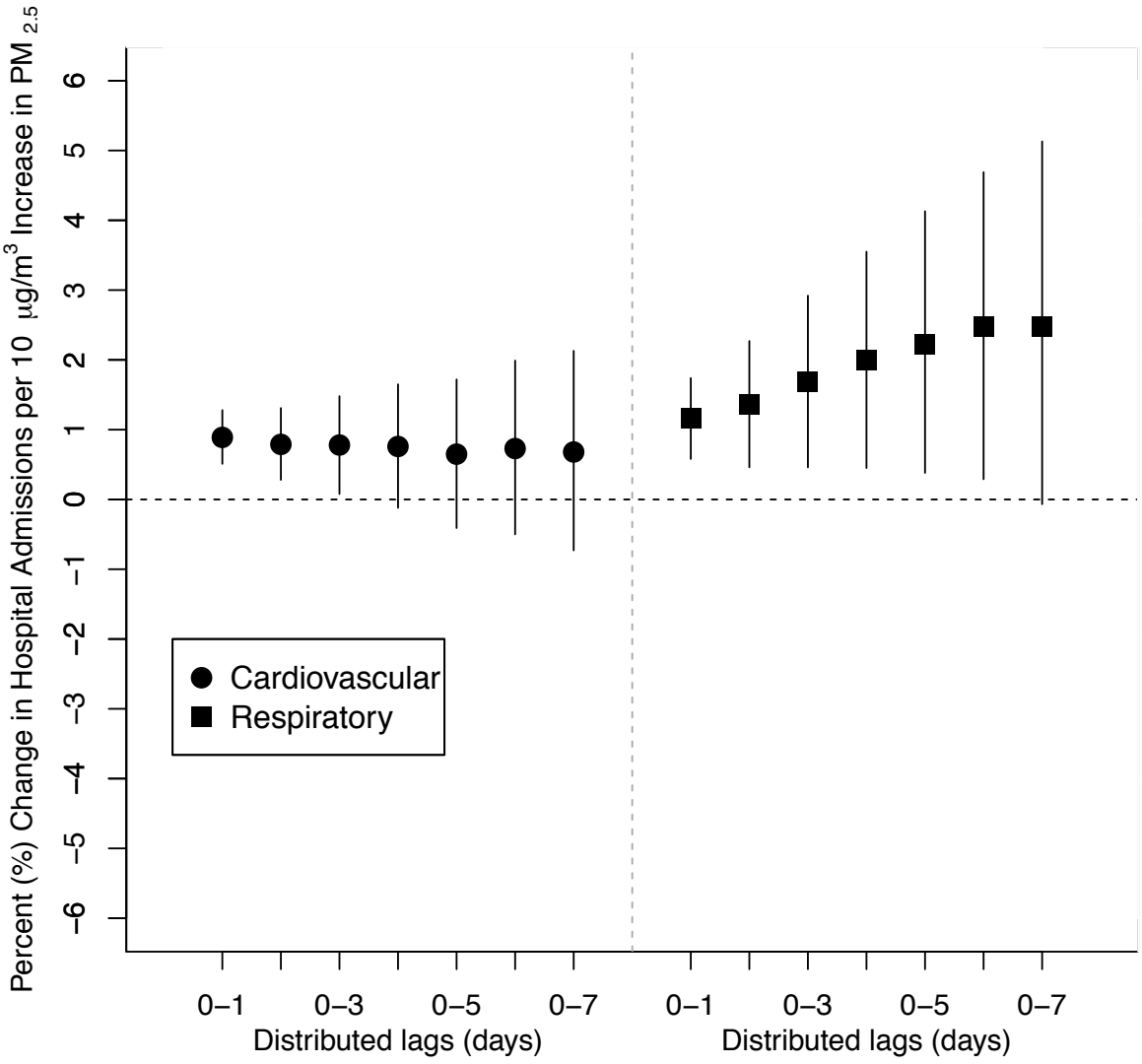

Percent (%) Change in Hospital Admissions per 10 μg/m3 Increase in PM 2.5
4
3
2
1
0
−1
−2
−3
−4
≤40% of pop. in urban areas (n = 67)
41−60% of pop. in urban areas (n = 140)
61−80% of pop. in urban areas (n = 235)
81−90% of pop. in urban areas (n = 113)
>90% of pop. in urban areas (n=153)
Cardiovascular
Respiratory
Health effect, Lag 0

Figure 3.


Percent (%) Change in Hospital Admissions per 10 μg/m3 Increase in PM 2.5
6
5
4
3
2
1
0
−1
−2
−3
−4
−5
−6
Cardiovascular
Respiratory
0–1
0–3
0–5
0–7
Distributed lags (days)
0–1
0–3
0–5
0–7
Distributed lags (days)